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EDITORIAL COMMENT

The 9p21 Locus and Coronary Heart Disease

Initiator, Promoter, or Precipitator?*

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Coronary heart disease (CHD), a major cause of worldwide morbidity/mortality (1), is a multifactorial, multistage disorder to which both environmental and genetic factors contribute (Fig. 1) (2). Despite methodologic advances, including genomewide association studies, progress in elucidating CHD genetics has been slow, and the number and impact of well-validated associations remain few and modest. One of the major successes in this effort has been the discovery of the CHD risk-associated locus at chromosome 9p21.3. First reported by several groups in 2007 (3–6), this association subsequently has been validated by multiple groups worldwide, across racial and geographic boundaries, and independent of traditional risk factors (7).

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The 9p21 risk variant is common, with nearly 50% carrying 1 high-risk allele (with a 20% to 40% increase in risk) and another 20% to 25% carrying 2 alleles (40% to 70% increase in risk) (7,8). Across a 58-kb region at 9p21.3, several single nucleotide polymorphisms (SNPs) exist that have been associated with various CHD phenotypes, including a clinical diagnosis of CHD, myocardial infarction (MI), angiographic coronary artery disease (CAD), or a mixture of these and others. More recent studies suggest that this phenotype should be refined to native coronary atherosclerosis but neither to restenotic disease nor MI per se (Fig. 1) (8–11). However, the mechanism of the risk association remains unclear. The 9p21.3 chromosome is located in a region that is devoid of transcribed genes but that includes a large antisense noncoding ribonucleic acid gene (ANRIL), which might act as a vascular growth regulatory element (12).

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Given its importance to CAD genetics, a better understanding of the role of 9p21 in coronary pathophysiology is of interest. In this issue of the *Journal*, Dandona et al. (13), from Ottawa, address the specific question of its impact on coronary disease burden.

Study Summary

Dandona et al. (13) test the hypothesis that the 9p21 variant promotes coronary atheroma progression. Two angiographically-phenotyped patient sets were studied: an early onset CAD group (men <55 years of age, women <65 years of age, with at least 1 stenosis >50%; n = 950), and a later-onset group (n = 764). Diabetic patients were excluded to enrich for genetic factors unique to CAD, and the population was restricted to patients of European heritage. The SNP marker chosen for the primary analysis was rs1333049 (3).

Results demonstrated a strong direct association of early 3-vessel disease with allele dosage (odds ratio: 1.45 per allele copy, $p = 4 \times 10^{-4}$) and, conversely, a strong inverse association with 1-vessel disease (odds ratio: 0.64, $p = 2 \times 10^{-5}$). The investigators then performed several supportive analyses: associations were replicated in the older age population, in the inaugural catheterization subgroup, in patients with early left main disease, in patients requiring bypass surgery, in the combined early and late cohorts, in analyses using the quantitative Gensini and Duke coronary scores, and in analyses using the linked 9p21 SNP rs9632884. A further analysis included a small number of cases with <50% stenosis (n = 143) and found a linear trend of allele frequency across 0- to 3-vessel disease. Finally, when CAD patients were stratified by number of diseased vessels and the association adjusted for baseline covariates, 9p21 did not predict MI.

Clinical interpretation and implications. The Ottawa investigators are to be congratulated on extending the exploration of 9p21. Whereas other recent studies have focused on comparisons between CAD and no-CAD populations, this study explores genetic associations within a CAD population. Their finding of a dose effect of the number of risk alleles for CAD severity in early onset disease could be replicated in a separate population of older patients and in multiple subset and combined-set analyses, indicating robust internal consistency. Given this, the authors suggest that the deposition of coronary atheroma mediates the risk of 9p21. An implication of this for future research is that a search for specific mechanisms should focus on atherogenesis, not on plaque instability or thrombosis. They further suggest that a clinical implication may be the use of 9p21 as a marker to complement traditional risk assessment in not only primary but also secondary CAD prevention.

These Ottawa data, added to other recent reports and to subgroup analyses from earlier studies, appear to conclusively debunk any direct link between 9p21 and MI susceptibility per se (5,8–12). Hence, the risk of 9p21 for MI must

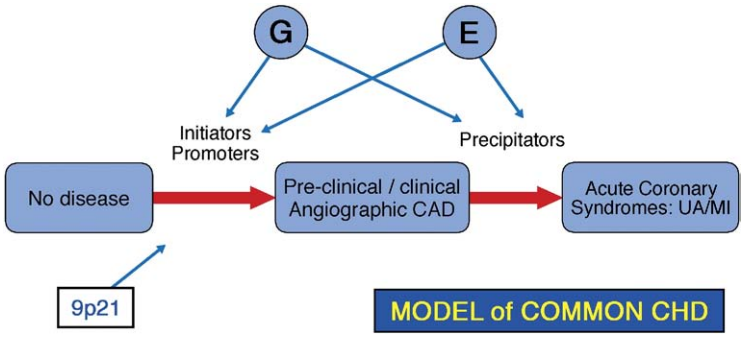

Figure 1 Genetic Model of Coronary Heart Disease

Modified from Horne et al. (9) and Hopkins et al. (2). CAD = coronary artery disease; CHD = coronary heart disease; E = environment; G = genes; MI = myocardial infarction; UA = unstable angina.

be explained indirectly through its association with atherogenesis and not by actual precipitation of MI (Fig. 1).

What potentially remains as controversial is the precise role of 9p21 in atherogenesis. Is 9p21 primarily an initiator/facilitator of CAD or an amplifier/accelerator/promoter (9)? The Ottawa study argues for the latter (13), whereas at least 3 earlier studies involving Asian and Caucasian populations lend support to the former (8,9,14,15). Which is correct, or could both be true? The authors offer 3 possible explanations for this discrepancy: 1) a skew in earlier studies to 1-vessel disease (with limited power for inter-CAD analyses); 2) use of different SNP markers for 9p21; and 3) inclusion of diabetic patients in earlier studies, hypothesizing that diabetes mellitus might interact to obscure the impact of 9p21 on CAD burden (16). None of these possibilities alone is intuitively compelling, and further explanations also should be considered, including population-specific differences (i.e., differing genetic background and environmental factors such as smoking, and use of >50% rather than >70% stenosis to define severe CAD [8,9]) as well as the play of chance. Nevertheless, when all of these factors are accounted for, 9p21 may finally be shown to play both roles in CAD development: limited data on risk allele frequency in 0-vessel disease separate it well away from 1- to 3-vessel disease in the Ottawa study (see their Fig. 3 [13]), supporting a role for 9p21 in CAD initiation, and minor numerical trends in our North American study associating 9p21 with disease burden might be amplified if controlled for the above factors (8). Future prospective studies will be required to definitively resolve this question.

The Ottawa study shares limitations with all cross-sectional, observational studies, including the potential for selection biases and uncontrolled confounding. Its implications apply strictly to the population and specific SNPs studied. Also, the suggestion that the 9p21 marker might be useful in both primary and secondary clinical risk assessment must be validated by prospective clinical studies. Nevertheless, this study importantly contributes to the growing and stage-specific understanding of the role of genetics in CHD pathogenesis: 9p21 acts to facilitate initiation of coronary atherosclerosis, not to precipitate MI (Fig. 1). Further, at least in a Canadian, nondiabetic, coronary disease population, dosage of the 9p21 rs1333049 high-risk variant also promotes and predicts CAD burden.

In conclusion, the answer to the question posed in the title of the relationship of 9p21 to CHD appears to be initiator, yes; promoter, probably; and precipitator, no.

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REFERENCES

1. Yusuf S, Reddy S, Ôunpuu S, Anand S. Global burden of cardiovascular diseases, part I: general considerations, the epidemiologic transition, risk factors, and impact of urbanization. Circulation 2001;104:2746–53.
2. Hopkins PN, Hunt SC, Wu LL. Family history and genetic factors. In: Wong ND, Black HR, Gardin JM, editors. Preventive Cardiology, a Practical Approach. New York, NY: McGraw-Hill, 2005:92–148.
3. McPherson R, Pertsemlidis A, Kavaslav N, et al. A common allele on chromosome 9 associated with coronary heart disease. Science 2007;316:1488–91.
4. Helgadottir A, Thorleifsson G, Manolescu A, et al. A common variant on chromosome 9p21 affects the risk of myocardial infarction. Science 2007;316:91–3.
5. Wellcome Trust Case-Control Consortium. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature 2007;447:661–78.
6. Samani NJ, Erdmann J, Hall AS, et al. Genomewide association analysis of coronary artery disease. N Engl J Med 2007;357:443–53.
7. Schunkert H, Goetz A, Braund P, et al. Repeated replication and a prospective meta-analysis of the association between chromosome 9p21.3 and coronary artery disease Circulation 2008;117:1675–84.
8. Anderson JL, Horne BD, Kolek MJ, et al. Genetic variation at the 9p21 locus predicts angiographic coronary artery disease prevalence but not extent and has clinical utility. Am Heart J 2008;156:1155–62.
9. Horne BD, Carlquist JF, Muhlestein JB, Bair TL, Anderson JL. Association of variation in the chromosome 9p21 locus with myocardial infarction versus chronic coronary artery disease. Circ Cardiovasc Genet 2008;1:85–92.

10. Hoppman P, Erl A, Turk S, et al. No association of chromosome 9p21.3 variation with clinical and angiographic outcomes after placement of drug-eluting stents. J Am Coll Cardiol Intv 2009;2:1449–55.
11. Horne BD, Anderson JL. Irrelevance of the chromosome 9p21.3 locus for acute cardiovascular events and restenosis. J Am Coll Cardiol Intv 2009;2:1156–7.
12. Broadbent HM, Peden JF, Lorkowski S, et al. Susceptibility to coronary artery disease and diabetes is encoded by distinct, tightly linked SNPs in the ANRIL locus on chromosome 9p. Hum Mol Genet 2008;17:806–14.
13. Dandona S, Stewart AFR, Chen L, et al. Gene dosage of the common variant 9p21 predicts severity of coronary artery disease. J Am Coll Cardiol 2010;56:479–86.
14. Hinohara K, Nakajima T, Takahashi M, et al. Replication of the association between a chromosome 9p21 polymorphism and coronary artery disease in Japanese and Korean populations. J Hum Genet 2008;53:357–9.
15. Hiura Y, Fukushima Y, Yuno M, et al. Validation of the association of genetic variants on chromosome 9p21 and 1q41 with myocardial infarction in a Japanese population. Circulation J 2008;72:1213–7.
16. Doria A, Wojcik J, Xu R, et al. Interaction between poor glycemic control and 9p21 locus on risk of coronary artery disease in type 2 diabetes. JAMA 2008;300:2389–97.

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